CLAIMS

What is claimed is:

1. A process for separating a first enantiomer of an optically active organic compound from a mixture comprising a first enantiomer and a second enantiomer, the process comprising:

(a) contacting a first solution comprising: (i) the first enantiomer; (ii) the second enantiomer; and (iii) a solvent, with a first resolving agent under conditions effective to precipitate from said first solution at least a portion of said second enantiomer, thereby forming a supernatant solution comprising at least a portion of said solvent and at least a portion of said first enantiomer;

(b) preparing said supernatant solution from step (a) for a second precipitation characterized in that: (i) said prepared supernatant solution does not contain any substantial amount of said first resolving agent; and (ii) a substantial portion of said first enantiomer in the supernatant solution is in a form suitable to form a precipitate with a second resolving agent; and

(c) subsequent to step (b), contacting said prepared supernatant solution with a second resolving agent under conditions effective to precipitate at least

a portion of said first enantiomer contained in said solution, said precipitate being characterized in that it does not contain any substantial amount of said second enantiomer.

2. The process of claim 1, wherein said preparing step (b) comprises:

(i) separating said supernatant solution from the precipitate;

(ii) optionally, replacing at least a portion of the solvent in said separated supernatant solution with at least one solvent of different polarity;

(iii) subsequent to step (ii) when step (ii) is present, contacting said supernatant solution with a sufficient amount of an immiscible liquid phase under conditions sufficient to cause a substantial portion of said first resolving agent remaining in the supernatant solution to migrate from the supernatant solution to said immiscible liquid phase, and whereby said contact places at least some of said first enantiomer in a condition suitable for forming a precipitate with a second resolving agent;

(iv) separating said supernatant solution from said immiscible liquid phase; and

(v) subsequent to step (iv) when step (ii) is present, optionally replacing at least a portion of the supernatant solution comprising the solvent of different polarity introduced in step (ii) with the same solvent comprising

the supernatant solution in step (i) or a solvent having the same or substantially similar polarity as the solvent comprising the supernatant solution of step (i).

3. The process of claim 1 wherein said first enantiomer in said steps (a) and (b) and said second enantiomer in step (a) are in acid form, and said solvent in step (a) is a polar, aprotic solvent.

4. The process of claim 3, wherein said preparing step (b) is the process comprising:

(i) separating the supernatant solution from the precipitate;

(ii) replacing at least a portion of the polar, aprotic solvent in the separated supernatant solution with an aprotic, non-polar solvent to produce a substantially non-aqueous, non-polar composition comprising said first enantiomer and said first resolving agent;

(iii) contacting said non-aqueous, non-polar composition with a sufficient amount of an aqueous acid solution under conditions sufficient to cause at least a substantial portion of said first resolving agent to migrate from said non-aqueous, non-polar composition to said aqueous acid solution and to convert substantially all of said first enantiomer in said non-aqueous, non-

polar composition to an acid form;

(iv) separating the non-aqueous, non-polar composition containing said first enantiomer in acid form from said aqueous acid phase; and

(v) replacing at least a portion the aprotic, non-polar, solvent in the separated non-aqueous, non-polar composition with a polar, aprotic solvent to produce said second solution comprising a polar, aprotic solvent and said first enantiomer.

5. The process of claim 4 wherein said supernatant solution of said preparing step (b) is substantially free of said first resolving agent.

6. The process of claim 5 wherein the precipitate formed in said contacting step (c) is substantially free of said second enantiomer.

7. The process of claim 6, further comprising recrystallizing the precipitate formed in contacting step (c).

8. The process of claim 7 further comprising isolating said recrystallized precipitate and converting it to a free acid form.

9. The process of claim 8, wherein said first enantiomer is (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid, said second enantiomer is (S) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid, said polar, aprotic solvent is acetonitrile, said non-aqueous, non-polar solvent is toluene, said first resolving agent is D-(+)-norephedrine, and said second resolving agent is L-(-)-norephedrine.

10. A process for isolation of a first enantiomer of an optically active organic acid compound in high optical purity from a composition comprising a first enantiomer and a second enantiomer of the compound, the process comprising:

(a) providing a first mother liquor comprising a first and a second optically active enantiomer in acid form dissolved in a polar, aprotic solvent;

(b) contacting the first mother liquor with a first resolving agent which forms with said second enantiomer a precipitate which is not more than sparingly soluble in said first mother liquor, said resolving agent further characterized in that it does not form with said first enantiomer any substantial amount of a precipitate from said first mother liquor;

(c) forming a first precipitate comprising said first resolving agent and

said second enantiomer;

(d) separating from said first mother liquor substantially all of said first precipitate;

(e) subsequent to step (d), forming a second mother liquor by replacing said polar, aprotic solvent in said first mother liquor with a non-polar, aprotic solvent;

(f) contacting said second mother liquor with an aqueous acid solution;

(g) forming a third mother liquor by replacing said non-polar, aprotic solvent of said second mother liquor with a polar, aprotic solvent;

(h) contacting said third mother liquor with a second resolving agent which forms with said first enantiomer a precipitate which is not more than sparingly soluble in said third mother liquor;

(i) forming a second precipitate comprising said first enantiomer and said second resolving agent; and

(j) separating substantially all of said second precipitate from said third mother liquor.

11. The process of claim 10 further comprising recrystallizing the precipitate of step

(j) from a polar, aprotic solvent.

12. The process of claim 11 further comprising slurrying said recrystallized product in a non-polar, aprotic solvent and converting it to a free acid form by treatment with aqueous HCl.

13. A process for separation of (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid from a mixture comprising (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid and (S) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid comprising:

(a) contacting a first mother liquor comprising a mixture of (R) and (S) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid in acid form dissolved in acetonitrile with (D)(+)-norephedrine;

(b) forming a first precipitate comprising (S) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid and (D)(+)-norephedrine;

(c) separating said first mother liquor from substantially all of said first precipitate;

(d) forming a second mother liquor by substantially replacing said acetonitrile in said first mother liquor with toluene;

(e) contacting said second mother liquor with aqueous HCl;

(f) subsequent to step (e), forming a third mother liquor by substantially replacing said toluene in said second mother liquor with acetonitrile;

(g) contacting said third mother liquor with with (L)(-)-norephedrine; and

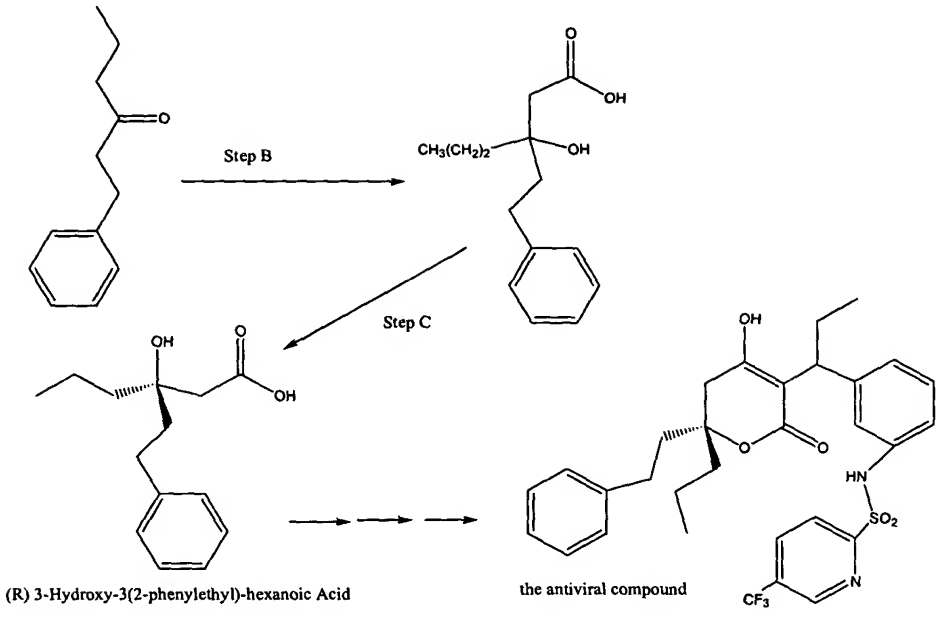
(h) forming a second precipitate comprising (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid and (L)(-)-norephedrine.

14. The process of claim 13 further comprising isolating said second precipitate formed in step (h) substantially free of said third mother liquor.

15. The process of claim 14 further comprising recrystallizing said isolated precipitate.

16. In a process comprising a multi-step synthetic scheme for synthesizing [R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide from (R) 3-hydroxy-3(2-phenylethyl)-hexanoic acid according to Scheme IV:

Scheme IV



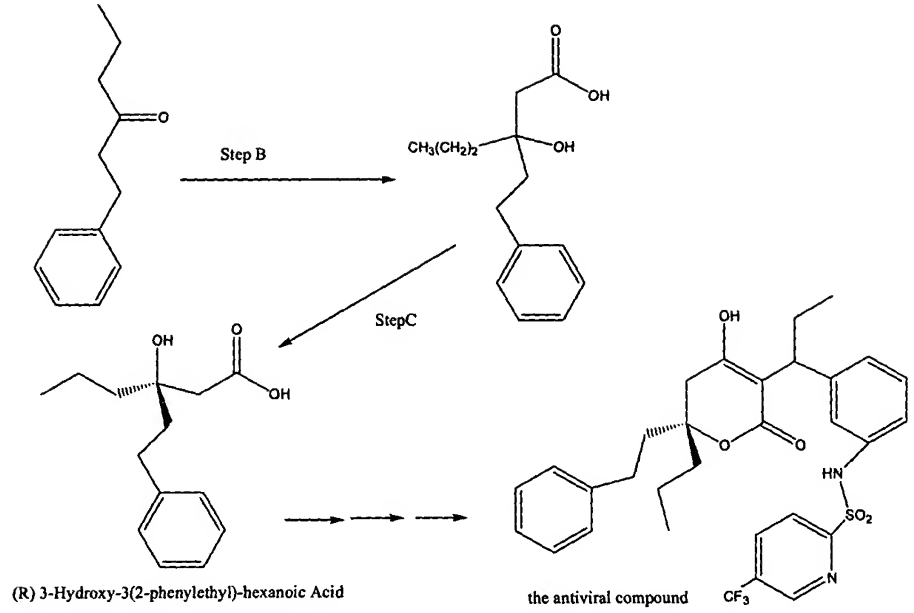
the improvement comprising Step "C" of Scheme IV comprising separation of (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid in enantiomeric excess from a mixture of (R) and (S) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid according to the process of claim 15.

17. The process of claim 16 wherein said separation Step C of Scheme IV is performed according to the process of claim 9.

18. The process of claim 16 wherein said separation Step C of Scheme IV is performed according to the process of claim 12.

19. In a process comprising a multi-step reaction sequence for synthesizing [R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (the antiviral compound) from (R) 3-hydroxy-3-(2-phenylethyl)-hexanoic acid according to Scheme IV:

Scheme IV



the improvement comprising performing Step "B" of Scheme IV comprising synthesis of racemic 3-hydroxy-3-(2-phenylethyl)-hexanoic acid, by a reaction comprising: contacting 1 phenyl-hexan-3-one with ethyl-bromoacetate in a high boiling, aprotic, polar solvent in the presence of zinc under Reformatsky reaction conditions.

20. The process of claim 19 wherein, during said Step "B" of Scheme IV, said solvent is maintained at a temperature of about 60°C to about 100°C.

21. The process of claim 20 wherein said solvent used in said Step "B" of Scheme IV comprises at least about 25 vol. % of a solvent selected from the group consisting of dimethoxymethane, dimethoxyethane, toluene, and combinations of two or more of these.

22. The process of claim 21 wherein said Step "C" of Scheme IV comprises separation of (R)3-hydroxy-3-(2-phenylethyl)-hexanoic acid in accordance with the process of claim 9.

23. The process of claim 21 wherein said Step "C" of Scheme IV comprises separation of (R)3-hydroxy-3-(2-phenylethyl)-hexanoic acid in accordance with the process of claim 15.

24. The process of claim 16 further comprising Step "B" of Scheme IV comprising synthesis of 3-hydroxy-3-(2-phenylethyl)-hexanoic acid racemate according to the process of claim 19.

25. The process of claim 16 further comprising Step "B" of Scheme IV comprising synthesis of 3-hydroxy-3-(2-phenylethyl)-hexanoic acid racemate according to the process of claim 20.

26. The process improvement of claim 16 further comprising Step "B" of Scheme IV comprising synthesis of 3-hydroxy-3-(2-phenylethyl)-hexanoic acid racemate according to the process of claim 23.

27. A process for synthesizing [R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide comprising the steps of:

(a) providing a racemic mixture of 3-hydroxy-3-(2-phenylethyl)-hexanoate ethyl acetate by reacting 1-phenyl-hexan-3-one with ethylbromoacetate under Reformatsky conditions;

(b) isolating (R)-3-hydroxy-3-(2-phenylethyl)-hexanoic acid in enantiomeric excess by saponification and reverse resolution of the racemate of step (a) to produce a resolved product;

(c) isolating the free acid from the resolved product of step (b);

(d) synthesizing a keto-ester comprising (R)-ethyl-5-hydroxy-3-oxo-5-phenyethyl-octanoate by reaction of said (R)-3-hydroxy-3-(2-phenylethyl)-hexanoic acid from step (c) with monoethyl malonate magnesium salt in the presence of 1,1'-carbonyldiimidazole;

(e) converting the keto-ester of step (d) to a hydroxy-lactone intermediate comprising (6R)-5,6-dihydro-4-hydroxy-6-[1-(2-phenylethyl)]-6-propyl-2H-pyran-2-one;

(f) converting the hydroxy-lactone intermediate of step (e) to the nitro-propenyl compound comprising [3α(R),6(R)]-5,6-dihydro-4-hydroxy-3-[(Z)-1-(3-nitrophenyl)-propenyl]-6-[1-(2-phenylethyl)]-6-propyl-2H-pyran-2-one and its enantiomer by condensing the hydroxy-lactone intermediate with m-nitropropiophenone in the presence of titanium tetrachloride and pyridine;

(g) stereospecifically reducing said nitro-propenyl compound from step (f) to the nitro-propyl compound comprising [3α(R),6(R)]-5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)-propyl]-6-[1-(2-phenylethyl)]-6-propyl-2H-pyran-2-one by contact with [(1,5-cyclooctadiene) rhodium(I)- 1,2-bis-(2R,5R)-dimethyl-

phospholano)benzene]tetrafluoroborate in the presence of hydrogen;

(h) reducing the nitro-propyl compound of step (f) to the amino-propyl compound comprising [3α(R),6(R)]3-[1-(3-aminophenyl)-propyl]-5,6-dihydro-4-hydroxy- 6-[1-(2-phenylethyl)]-6-propyl-2H-pyran-2-one by contact with a palladium catalyst in the presence of hydrogen; and

(i) reacting the amino propyl compound of step (g) with 5-(trifluoromethyl)-2-pyridinesulfonyl chloride in the presence of pyridine followed by acidification of the mixture, thus providing [R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide.